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| GIBBS, TERRA C |

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| 1635 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/525,312 | DORN ET AL. | |
| | Examiner | Art Unit | |
| | Terra C. Gibbs | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 18-20* is/are rejected.

7)☒ Claim(s) *17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *October 3, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office Action is a response to Applicant's Preliminary Amendment filed February 22, 2005.

Claims 3-11, 15, and 20 have been amended.

Claims 1-20 are pending in the instant application.

***Election/Restrictions***

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

According to the guidelines in Section (f)(i)(a) of Annex B of the PCT Administrative Instructions, the special technical feature as defined by PCT Rule 13.2 shall be considered to be met when all the alternatives of a Markush-group are of similar nature. For chemical alternatives, such as the claimed VEGF receptor genes, the Markush group shall be regarded as being of similar nature when:

(A) all alternatives have a common property or activity and

(B)(1) a common structure is present, i.e., a significant structure is shared by all of the alternatives or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to an art-recognized class of compounds in the art to which the invention pertains.

The target genes listed in claims 5, 6, 16, and 19 do not meet the criteria of (B)(1), where a common structure is present, i.e., a significant structure is shared by all

of the alternatives. The target genes listed in claims 5, 6, 16, and 19 do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure. Accordingly, unity of invention between the target genes listed in claims 5, 6, 16, and 19 is lacking and each target gene claimed is considered to constitute a special technical feature.

Furthermore, claims 5, 6, 16, and 19 are subject to restriction since it is not considered to be a proper genus/Markush. See MPEP 803.02- PRACTICE RE MARKUSH-TYPE CLAIMS - If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction. Since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

Claims 5, 6, and 19 specifically claim methods of using double-stranded RNA that inhibit the expression of specific target genes. Claim 16 specifically claims

pharmaceutical compositions comprising double-stranded RNA that inhibit the expression of specific target genes. The instant dsRNA targeted to specific target genes are considered to be unrelated, since each dsRNA targeted to specific target gene and method of using each dsRNA targeted to specific target gene claimed is structurally and functionally independent and distinct for the following reasons: each target gene has a unique nucleotide sequence, and each target gene has specific double-stranded RNA which targets a different and specific region of its respective target (per Applicant's Tables 1-4 in the specification). As such, the Markush/genus of target genes in claims 5, 6, 16, and 19 is not considered to constitute a proper genus, and is therefore subject to restriction. Furthermore, a search of more than one (1) of the dsRNA targeted to specific target gene and method of using dsRNA targeted to specific target gene claimed in claims 5, 6, 16, and 19 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed target gene sequences. In view of the foregoing, one (1) dsRNA targeted to specific target gene and method of using dsRNA targeted to specific target gene is considered to be a reasonable number of sequences for examination. Accordingly, applicants are required to elect one (1) target gene from claims 5, 6, 16, and 19. Note that this is not a species election.

Additionally, the double-stranded RNAs listed in claim 17 do not meet the criteria of (B)(1), where a common structure is present, i.e., a significant structure is shared by all of the alternatives. The double-stranded RNAs listed in claim 17 do not meet the criteria of (B)(1), as they do not share, one with another, a common core structure.

Accordingly, unity of invention between the double-stranded RNAs listed in claim 17 is lacking and each double-stranded RNA claimed is considered to constitute a special technical feature.

Furthermore, claim 17 is subject to restriction since it is not considered to be a proper genus/Markush. See MPEP 803.02- PRACTICE RE MARKUSH-TYPE CLAIMS - If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require restriction. Since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.

Claim 17 specifically claims pharmaceutical compositions comprising double-stranded RNA that inhibit the expression of specific target genes represented by SEQ ID NOs: 7, 9, 11, 13, 15, 17, and 22. The double-stranded RNAs are considered to be unrelated, since each double-stranded RNA claimed is structurally and functionally

independent and distinct for the following reasons: each double-stranded RNA has a unique nucleotide sequence, and each double-stranded RNA targets a different and specific region of its respective target gene (per Applicant's Tables 1-4 in the specification). As such, the Markush/genus of double-stranded RNA in claim 17 is not considered to constitute a proper genus, and is therefore subject to restriction. Furthermore, a search of more than one (1) of the double-stranded RNAs claimed in claim 17 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed double-stranded RNA. In view of the foregoing, one (1) double-stranded RNA is considered to be a reasonable number of sequences for examination. Accordingly, applicants are required to elect one (1) double-stranded RNA, selected from SEQ ID NOs: 7, 9, 11, 13, 15, 17, and 22 as recited in claim 17. Note that this is not a species election.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, this lack of unity is supported and restriction for examination purposes as indicated is proper.

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During a telephone conversation with Applicant's Representative, John Prince, on or around January 3, 2007, a provisional election was made **with traverse** to prosecute the Mob-5 target gene from claims 5, 6, 16, and 19 and SEQ ID NO:22 from claim 17. Applicant must make affirmation of this election in replying to this Office

Action.

It is noted that claim 16 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Additionally, target genes recited as purine receptors P1 or P2; Galanin R1 receptor; IL-24; IL-20Rα; IL20Rβ; MMP7; $P_2X_3$; and $P_2X_2$, and SEQ ID NOs: 7, 9, 11, 13, 15, and 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-15 and 17-20 have been examined on the merits.

***Priority***

Receipt is acknowledged of foreign papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Information Disclosure Statement***

Applicant's information disclosure statement filed October 3, 2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR §1.97.

Accordingly, the Examiner has considered the information disclosure statement, and a signed copy is enclosed herewith.

***Specification***

The Specification is objected to for the reason(s) discussed below: Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "**said**," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

***Nucleotide and/or Amino Acid Sequence Disclosure***

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 1.821 through 1.825 for the reason(s) set forth below. Applicant's attention is directed to the regulations, published at 1114 OG 29, May 15, 1990 and at 55 Fed. Reg. 18230, May 1, 1990.

This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c). Furthermore, a copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e). It is the duty of the applicant to fully comply with the sequence rules of 37 CFR § 1.821-1.825.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-8, 11-15, and 18-20 are provisionally rejected under the judicially created doctrine of double patenting over claims 1, 2, 4, 5, and 25 of copending Application No. U.S. Publication No. **20060128644** ('644). This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 3-8, and 18-20 of the instant application are drawn to a method of treating or ameliorating neurological disorders in a subject in need thereof,

comprising administering a double stranded RNA (dsRNA) targeted to the Mob-5 gene, wherein said dsRNA inhibits the expression of the target gene, wherein the neurological disorder is chronic pain (see claim 3). Claims 11-15 of the instant application are drawn to a method of treating or ameliorating neurological disorders in a subject in need thereof, comprising administering a dsRNA targeted to the Mob-5 gene, wherein said dsRNA inhibits the expression of the target gene, and wherein the dsRNA comprises a 3' overhang; wherein the overhang contains at least one modified nucleotide; wherein the overhang comprises at least one 2'-MOE modified nucleotide; wherein the overhang comprises 4 uracils; and wherein the dsRNA comprises at least one phosphorothioate linkage.

Claims 1, 2, 4, 5, and 25 of copending Application No. '644 are drawn to a method of treating or ameliorating chronic neuropathic pain in a subject in need thereof, comprising administering a Mob-5 modulator, wherein the modulator is a double stranded RNA (dsRNA) targeted to the Mob-5 gene, and wherein said dsRNA inhibits the expression of the target gene. It is noted that the dsRNA targeted to the Mob-5 gene disclosed by '644 comprises a 3' overhang; wherein the overhang contains at least one modified nucleotide; wherein the overhang comprises at least one 2'-MOE modified nucleotide; wherein the overhang comprises 4 uracils; and wherein the dsRNA comprises at least one phosphorothioate linkage (see pages 26 and 27, last paragraph and first paragraph, respectively, and Table 8).

Claims 1, 2, 4, 5, and 25 of co-pending application '644 embrace the method of treating or ameliorating neurological disorders in a subject in need thereof, comprising

administering a double stranded RNA (dsRNA) targeted to the Mob-5 gene, wherein said dsRNA inhibits the expression of the target gene, and wherein the neurological disorder is chronic neuropathic pain as instantly claimed and thus fully encompasses the subject matter of the instant application.

This is a provisional obviousness-type double patenting rejection.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 18-20 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 12, 14, and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18-20 provides for the "use of a double stranded RNA", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 4 is indefinite because it recites in the preamble, "The method according to claim 1 wherein said chronic pain". There is insufficient antecedent basis for this limitation in the claim because claim 1 makes reference to "neurological disorders", not "chronic pain".

Claims 12 and 14 are indefinite because they recite in their preambles, "The method according to claim 10 wherein the overhang". There is insufficient antecedent basis for this limitation in the claim because claim 10 never makes reference to an overhang.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-15 and 19 are drawn to a method of treating or ameliorating neurological disorders in a subject in need thereof, comprising administering a double stranded RNA (dsRNA) targeted to the Mob-5 gene, wherein said dsRNA inhibits the expression of the target gene.

The specification teaches a single dsRNA comprising an antisense and sense strand targeted to rat Mob-5 (see Table 4; SEQ ID NOs: 21 and 22). The specification also teaches that the gene encoding Mob-5 has GenBank Accession No. AAF75553 (see page 13, second full paragraph). The specification also teaches that the human homolog to Mob-5 is known as "interleukin-24", "Melanoma differentiation-associated gene 7 protein (MDA-7)", and "suppression of tumorigenicity 16" (see page 13, second full paragraph). The specification further teaches genes encoding members of the Mob-5 family have GenBank Accession Nos. AAA91780 or NM_AAB69171, for example, (see page 13, second full paragraph). The prior art teaches Mob-5 and homologs of Mob-5 with different GenBank Accession Numbers. For example, the prior art teaches GenBank Accession Number AAH09681- Interleukin 24 [Homo sapiens]; NP_444325- Interleukin 24 [Mus musculus]; NP_579845- Interleukin 24 [Rattus norvegicus]; AAP35820- Interleukin 24 [Homo sapiens]; AAL34146- Interleukin 24 [Homo sapiens]; AAA91780- MDA-7; AAK52589- suppression of tumorigenicity 16 protein [Homo sapiens] NP_444325- interleukin 24 [Mus musculus]; Q13007- Interleukin-24 precursor (Suppression of tumorigenicity 16 protein) (Melanoma differentiation-associated gene 7 protein) (MDA-7); and AAK52590- melanoma differentiation associated gene-7 [Mus musculus]. However, neither the instant specification, nor the prior art describe dsRNA

targeted to the Mob-5 gene, other than SEQ ID NOs: 21 and 22, wherein said dsRNA are used as pharmaceutical compositions in a method of treating or ameliorating a neurological disorder in a subject in need thereof.

At the outset, it is noted that the rejected claims do not recite any sequence identifier relating to Mob-5. This sequence is thus considered to be defined by its function (i.e. the activity of Mob-5) rather than by any one specific structure. Accordingly, the claims embrace dsRNA pharmaceutical compositions targeted to Mob-5, or any such molecule with analogous Mob-5 activity, known or yet to be discovered, along with any isoform or allele present within this species, precursor forms, partial forms, homologs, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain Mob-5 activity. For further explanation of preferred embodiments of the Mob-5 target gene, see the instant specification at page 13, second full paragraph.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of

complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention.

Further, See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between

that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

In order to synthesize the pharmaceutical compositions comprising a dsRNA targeted to Mob-5 and practice the methods claimed, one of skill would first need the sequence of the Mob-5. Although the instant specification teaches a dsRNA targeted to rat Mob-5, the claims embrace compositions directed to *any* sequence of Mob-5, or any such molecule with analogous Mob-5 activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain Mob-5 activity. Apart from further experimentation, the skilled artisan would not have been able to predict the structures of the full scope of the claimed compositions encompassed by the instant invention, particularly in the absence of any teaching by way of structure or reference to active domains or regions. The genus is not immediately envisioned because the genus of pharmaceutical compositions comprising dsRNA targeted to Mob-5 is considered to include not only the sequences taught in the instant invention and the prior art, but also any such molecule with analogous Mob-5 activity, known or yet to be discovered. However, the distinguishing characteristics of the claimed genus are not considered to be described herein, or in the prior art. Thus, because one of skill in the art could not envision any pharmaceutical compositions comprising a dsRNA targeted to Mob-5 used to treat or ameliorate a neurological disorders in a subject in need thereof, other than those described in the instant

specification, one of skill would not be convinced that applicants were in possession of any pharmaceutical compositions comprising a dsRNA targeted to Mob-5 sequences that are heretofore undescribed.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

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Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to treat or ameliorate chronic neuropathic pain in a subject in need thereof, comprising intrathecally administering a dsRNA targeted to Mob-5, wherein the dsRNA comprises SEQ ID NO:21 and SEQ ID NO:22, and wherein the dsRNA inhibits Mob-5 gene expression, does not reasonably provide enablement for a method to treat or ameliorate *any* neurological disorder(s) in a subject in need thereof, comprising intrathecally administering *any* dsRNA targeted to *any* Mob-5, and wherein the dsRNA inhibits Mob-5 gene expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These

factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are drawn to a method to treat or ameliorate *any* neurological disorder(s) in a subject in need thereof, comprising intrathecally administering *any* dsRNA targeted to Mob-5, and wherein the dsRNA inhibits Mob-5 gene expression.

The nature of the claimed invention, therefore, requires the knowledge of using dsRNA to inhibit gene expression wherein the result of such inhibition treats or ameliorates any neurological disorder in a subject.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that SEQ ID NOs: 21 and 22 are annealed together to give the siRNA targeted to rat Mob-5 (see page 20 and Table 4). The specification teaches the effects of Mob-5 siRNA on mechanical hyperalgesia and mechanical allodynia in a rat model of neuropathic pain. Specifically, the specification teaches that SEQ ID NOs: 21 and 22 are intrathecally administered to a rat model of neuropathic pain and showed diminished pain responses when compared to missence Mob-5 siRNA control (see Examples 9 and 10).

Although the specification teaches that dsRNAs targeted to Mob-5 represented

by SEQ ID NOs: 21 and 22 can be used to treat chronic neuropathic pain in a rat model for neuropathic pain, the specification does not teach any other neurological disorder other than chronic pain. Furthermore, the specification does not teach any other dsRNAs targeted to Mob-5 that can be used in the methods as claimed.

The claims encompass a method to treat or ameliorate *any* neurological disorder(s) in a subject in need thereof, comprising intrathecally administering *any* dsRNA targeted to *any* Mob-5. The claims therefore encompass dsRNA pharmaceutical compositions targeted to Mob-5, or any such molecule with analogous Mob-5 activity, known or yet to be discovered, along with any isoform or allele present within this species, precursor forms, partial forms, homologs, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain Mob-5 activity. However, the specification does not teach dsRNA targeted to variants of Mob-5, nor does the specification teach any dsRNA targeted to homologs of Mob-5 which can be used in the methods as claimed.

The specification provides no universal correlation that any neurological disorder would be treated or ameliorated using any dsRNA targeted to any Mob-5 sequence. The specification provides no structure/function correlation between the disclosed dsRNA targeted to Mob-5 (SEQ ID NOs: 21 and 22) and treating or ameliorating a neurological disorder for the ordinary artisan to be able to predict which other dsRNA molecules targeted to Mob-5 encompassed in the claims might be predictably associated with the claimed methods. There is no teaching by way of structure or reference to active domains or regions within the Mob-5 gene. Therefore, the skilled

artisan would be unable to predictably correlate any other structural correlation of the dsRNA with treating or ameliorating a neurological disorder in a subject in need thereof.

The specification provides no predictable association that any dsRNA, in any Mob-5 gene, in any subject, will treat or ameliorate any neurological disorder. No common element or attributes of the dsRNA targeted to Mob-5 are disclosed which would permit selection of dsRNAs as pharmaceutical compositions for treating or ameliorating a neurological disorder. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations are provided. Further, these claims expressly encompass dsRNA pharmaceutical compositions targeted to Mob-5, or any such molecule with analogous Mob-5 activity, known or yet to be discovered, along with any isoform or allele present within this species, precursor forms, partial forms, homologs, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain Mob-5 activity. No written description of Mob-5 variants, Mob-5 homologs, or families of proteins that retain Mob-5 activity, which are associated with any neurological disorder are described in the specification. Additionally, the specification provides no evidence that any dsRNA targeted to Mob-5 provides a predictable association with a neurological disorder. Although the specification teaches that SEQ ID NOs: 21 and 22 can be successfully used in a method of treating or ameliorating chronic pain, this one disclosed dsRNA targeted to Mob-5 is not representative of the genus because the genus is highly variant.

The state of the prior art and the predictability or unpredictability of the art:

The prior art teaches that the use of dsRNA, including siRNA, in gene therapy is highly unpredictable. For example, Downward, J. (BMJ, 2004 Vol. 328:1245-1428) addresses the unpredictability and the problems faced in the siRNA art with the following statements: "Although a big improvement on previous methods, RNA interference has its limitations. Not every sequence works - most researchers get a success rate of about one in three. In addition, although the effects are generally thought to be highly sequence specific, some question marks remain as to whether or not some of the effects seen are "off target"" (see page 1246, last paragraph).

Paroo et al. (Trends in Biotechnology, 2004 Vol. 22:390-394) address the unpredictability associated with siRNA therapy with the following statements: "In contrast to the great success of synthetic siRNA in mammalian cell culture, there have been few reports employing synthetic siRNA in animals. Developing siRNA for efficient gene silencing *in vivo* is likely to be more challenging and many issues must be addressed before use in animals can become routine". Paroo et al. also state, "Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires the analysis and *de novo* determination of those dsRNA targeted to Mob-5 that are successfully delivered to target sites in appropriate cells and/or tissues such that

inhibition of Mob-5 gene expression is achieved and treating or ameliorating a neurological disorder is resultant. As neither the prior art nor the specification provide guidance as to how the Mob-5 gene is predictably associated with a neurological disorder, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible dsRNA targeted to Mob-5 for its therapeutic benefit for the treatment or amelioration of a neurological disorder is unpredictably undertaking in itself, with each of the many intervening steps, not providing any guarantee of success. Since the specification provides only one example of a dsRNA targeted to Mob-5 that is successfully delivered to target sites in appropriate cells and/or tissues such that inhibition of Mob-5 gene expression is achieved and treating or ameliorating chronic pain is resultant, and since resolution of the various complications in regards to targeting a particular gene in a living organism is unpredictable, one of skill in the art would have been unable to practice the invention claimed, commensurate in scope, without engaging in undue trial and error experimentation.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Roberts et al. (Gene Ther Mol. Biol., 1999 Vol. 4:45-58).

Claim 18 is drawn to the use of a double-stranded RNA for the preparation of a medicament for the treatment of chronic pain. Claim 20 is dependent on claim 18 and includes all the limitations of claim 18 with the further limitations wherein said chronic pain is osteoarthritis pain.

Roberts et al. disclose a double-stranded hammerhead ribozyme targeted against a cellular mRNA encoding a matrix metalloproteinase, stromelysin, where stromelysin expression has been linked to the pathogenesis of human osteoarthritis (see Abstract, Figure 2, Figure 3, and page 9, part E.).

The Examiner would like to note that the term "the use of" denotes an intended use, which holds no patentable weight since a method of intended use does not change the double-stranded RNA composition itself. Therefore, given the teachings of Roberts et al., one of ordinary skill in the art would expect success at using the double-stranded RNA for the preparation of a medicament for the treatment of chronic pain as instantly claimed.

Therefore, Roberts et al. anticipate claims 18 and 20.

***Conclusion***

Claim 17 is objected to because the claim contains nonelected subject matter, but would be allowable if rewritten to remove the nonelected subject matter. Claim 17 is considered to be free of the prior art since the prior art does not teach or fairly suggest a pharmaceutical composition comprising an effect amount of at least one double-stranded RNA, said double stranded RNA comprising a strand of SEQ ID NO:22.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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